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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Bachovchin *et al.*	Examiner:	Lukton, D.
Serial No.:	08/950,542	Art Unit:	1653
Filed:	October 15, 1997		
For:	INHIBITORS OF DIPEPTIDYL-AMINOPEPTIDASE TYPE IV		

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Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

September 4, 2003

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Applicant appeals to the Board of Patent Appeals and Interferences (the "Board") from the Examiner's rejection of claims 35, 36, 39-43, and 46-51. A Notice to this effect was filed pursuant to 37 C.F.R. § 1.191(a) on April 8, 2003.

Filed herewith is a Petition under 37 C.F.R. § 1.136 for a three (3) month extension of time, from June 15, 2003, up to and including September 15, 2003, to file this Appeal Brief (the "Brief"). Applicant thus submits that the present Response is timely submitted on Thursday, September 4, 2003. Pursuant to 37 C.F.R. § 1.192(a), this Brief is being filed in triplicate.

Real Parties in Interest

The real parties in interest in this case, as a result of Assignment from the inventors, are New England Medical Center Hospitals, Inc. and Trustees of Tufts College. The assignment of Andrew G. Plaut's interest in the present application to New England Medical Center Hospitals, Inc. is recorded in the Patent and Trademark Office at Reel 6048, Frame 0464. The assignment of William W. Bachovchin's and George R. Flentke's interests in the present application to the Trustees of Tufts College is recorded in the Patent and Trademark Office at Reel 7635, Frame 0428.

Point Therapeutics, Inc., of Boston, Massachusetts, is a licensee of the present application

Related Appeals and Interferences

No other appeals or interferences are known to the Appellant or the Appellant's legal representative that will directly affect or be directly affected by the Board's decision in this appeal. Similarly, no such appeals or interferences are known that may have a bearing on the Board's decision in this appeal.

Status of Claims

Claims 35, 36, 39-43, and 46-51 are pending and stand rejected. The rejection of claims 35, 36, 39-43, and 46-51 is hereby appealed. A listing of pending claims is provided as **Attachment I**.

Status of Amendments

The claims were last amended in a Response under 37 C.F.R. § 1.116, filed on April 25, 2002. The amendment was entered by the Examiner, and the amended claims were rejected in an Office Action, mailed December 31, 2002. The claims on appeal are those resulting from the amendment filed April 25, 2002, and rejected by the Examiner.

Summary of Invention

The present invention is directed to boroproline-containing peptides, which are inhibitors of dipeptidyl-aminopeptidase Type IV (DPIV). Specifically, the claims are directed to mixtures of stereoisomers of boroproline-containing peptides which are enriched in the stereoisomer with the carbon atom bearing boron being in the L-configuration. These mixtures are at least 96% pure with respect to the stereoisomer with the carbon bearing boron being in the L-configuration. These compounds have been found useful in the treatment of diseases including AIDS, neutropenia, and other hematopoietic disorders.

Issues

There are three issues on appeal, namely

(1) whether claims 35, 36, 39-43, and 46-51 lack enablement under 35 U.S.C. § 112, first paragraph;

(3) whether claims 35, 36, 39, 41, 42, and 46-49 are unpatentable under 35 U.S.C. § 103 over Bachovchin *et al.* (*J. Biol. Chem.* 265:3738, 1990).

Grouping of Claims

As to the rejection of claims 35, 36, 39, 41, 42, and 46-49, these claims stand or fall together.

As to the rejection of claim 40, 43, 50, and 51, these claims stand or fall together.

Argument

The Examiner has rejected the appealed claims for lack of enablement in Office Actions mailed March 15, 2001, October 26, 2001, and December 31, 2002, and in the Advisory Action mailed August 13, 2002.

The Examiner has rejected the appealed claims for lack of written description in Office Actions mailed March 15, 2001, October 26, 2001, and, December 31, 2002, and in the Advisory Action mailed August 13, 2002.

The Examiner has rejected the appealed claims as being unpatentable over Bachovchin *et al.* (*J. Biol. Chem.* 265:3738, 1990) in Office Actions mailed April 7, 1998, December 4, 1998, June 24, 1999, July 24, 2000, March 15, 2001, October 26, 2001, and December 31, 2002, and in the Advisory Actions mailed February 1, 2000, and August 13, 2002.

Applicant respectfully disagrees with the Examiner for reasons already provided (see previously filed Responses to Office Actions filed September 4, 1998, April 2, 1999, December 22, 1999, January 23, 2001, August 15, 2001, April 25, 2002, each of which is incorporated herein by reference) and further for reasons that are discussed below.

I. Rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement is unwarranted given the enabling disclosure in the specification for separating the diastereomers of boroproline-containing peptides.

Claims 35, 36, 39-43, and 46-51 stand rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to

Summary of the Issues Raised by the Examiner

Under 35 U.S.C. § 112, first paragraph, the enablement requirement is satisfied if one reasonably skilled in the art could make and/or use the invention defined by the claims from the disclosures in the patent application coupled with information known in the art without undue experimentation. See MPEP § 2164.01. The courts have also articulated a similar standard. See U.S. v. Teletronics, Inc., 8 USPQ2d 1217, 1223 (Fed.Cir. 1988). In addition, the Courts have articulated certain factors which must be considered in determining whether the claimed invention is enabled by the disclosure provided in the patent application as filed. These eight factors, commonly known as the Wands factors, include 1) unpredictability of the art, 2) state of the art, 3) number of working examples, 4) amount of guidance, 5) nature of the invention, 6) breadth of the claimed invention, 7) level of skill in the art, and 8) quantity of experimentation required. See In re Forman, 230 USPQ 546 (Bd.Pat.App.&Int. 1986); In re Wands, 8 USPQ2d 1400 (Fed.Cir. 1988). Each of these factors must be considered and weighed in turn to determine whether the Applicant has fulfilled the enablement requirement as set out in 35 U.S.C. § 112, first paragraph.

According to the Examiner, "the specification does not enable a skilled organic chemist to obtain the requisite isomer with a purity of 96% or greater." First, the Examiner points out that the specification only discloses two species, Pro-boroPro and Ala-boroPro, and two different procedures for separating the stereoisomers of each of these species. The procedure on page 15, line 3+ for separating L-Ala-D-boroPro from L-Ala-L-boroPro by eluting with MeOH/EtOH on silica gel is erroneous, and the procedure on page 21 for separating L-Pro-L-boroPro from L-Pro-D-boroPro be eluting with a water/acetonitrile gradient on a C_{18} HPLC column is correct. The Examiner points to the existence of cis and trans isomers of each of these compounds as the reason for the erroneous conclusion that the silica gel chromatography technique described on page 15 is unsuccessful in separating the diastereomers of Ala-boroPro. The Examiner concludes that since the specification provides two procedures for separating the diastereomers, one of which is errroneous and one of which is correct, the ordinary chemist reading the specification would be confused; and therefore, the specification does not provide an enabling disclosure for separating the diastereomers.

[illegible] of stereoisomers using the procedure described on page 21. The procedure, which begins on

page 21 at line 12, discloses the use of high pressure liquid chromatography (HPLC) to separate L-Pro-D-boroPro from L-Pro-L-boroPro. When this procedure is followed, "an isomeric purity of about 99-6% for each isomer" is obtained. Given this enabling disclosure, Applicant requests that the Examiner's rejection be overturned.

In fact, the Examiner has even conceded that the specification is enabling for Pro-boroPro, which is the exemplary dipeptide purified in the HPLC procedure of page 21. However, the Examiner goes on to erroneously conclude that since the specification only provides an enabling disclosure for Pro-boroPro, the specification is only enabling for that species. One of skill reading the description of the HPLC method would know that not only would the method successfully separate the diastereomers of Pro-boroPro but that the method would also be effective at separating the diastereomers of other boroproline-containing dipeptides and oligomers. In essence, the Examiner is not giving one of ordinary skill art reading the specification enough credit. One of ordinary skill in this art would have at least a doctorate in chemistry and would appreciate the fact that the HPLC method could be used for not only purifying stereoisomers of Pro-boroPro but other dipeptides and oligomers containing boroProline. Although certain details may need to be optimized for a particular boroPro-containing peptide, this type of optimization would not require undue experimentation and is regularly undertaken by chemists seeking to purify derivatives or analogs of compounds that have been successfully purified by a known method. Therefore, Applicant has not only provided an enabling disclosure for Pro-boroPro dipeptides but has also provided an enabling disclosure for the claimed genus of boroPro-containing compounds with the recited purity.

The Examiner has also stated that the claimed genus is of infinite size and gives an example of a claimed compound of claim 35 wherein A' is a polymer of leucine. The Examiner states in his rejection:

> "For this case, would a C_{18} matrix necessarily provide a better separation than a silica matrix? The claimed genus of compounds runs the gamut from highly polar to very hydrophobic. Even if the skilled chemist were to conclude that people should selectively avoid procedures that are recommended in patent applications, the specification provides no guidance as to which procedures to [illegible]"

not only dipeptides of boroproline but also peptides of greater length. However, the specification

does provide an enabling disclosure for boroproline-containing peptides greater than two amino acids in length and enriched in the L-isomer of boroproline. One of ordinary skill in the art reading the specification would be taught how to prepare boroproline-containing peptides of a length greater than two residues, without undue experimentation. The Examiner in his rejection has not met his burden of proving that the disclosure of the present application is not enabling for peptides greater than two amino acids in length. The specification teaches how one of ordinary skill in the art can obtain boroProline-containing peptides enriched in L-boroProline residues and the Examiner has provided no concrete evidence to show that the disclosure is not enabling of such peptides. Just to give but one example of how a skilled chemist might go about making a longer peptide with the required stereochemical purity, the starting material, boroproline, or the intermediate, dipeptide or tripeptide, in the synthesis of a longer peptides could be purified to the desired steroechemical purity using the procedure described on page 21 of the specification. The subsequent amino acids could then be added onto the purified compound to yield a longer peptide with the required stereochemical purity at the alpha-carbon of the boroproline residue. The idea of purifying an intermediate to the desired stereochemical purity before the small differences between stereoisomers such as diastereomers is overwhelmed by other functional groups of the molecule is well known in the art of synthetic organic chemistry and peptide chemistry. Therefore, one of ordinary skill in the art would be able to prepare a longer boroproline-containing peptide without undue experimentation based on the teachings in the specification. As discussed before, the Examiner is not giving one of skill in the art enough credit in being able to read the specification and apply the teachings to any compounds expect those which are explicitly disclosed. Clearly, this is not the proper legal standard for enablement. Applicant respectfully submits that the specification is enabling under 35 U.S.C. § 112, first paragraph, for not only dipeptides but also much longer peptides.

Applicant points out that the level of skill in this art is very high, indeed. Applicant submits that the Examiner has applied an incorrect standard and has attributed an inappropriately low level of skill to the person of ordinary skill in this art. The proper legal standard for enablement allows one of ordinary skill in the art to apply what is commonly known in the art to

other boroProline containing peptides.

The Examiner has also brought up extraneous issues regarding the enablement of the claimed invention. For instance, the Examiner has stated that since the dipeptides come in *cis* and *trans* forms and the specification does not provide for the separation of the cis and trans forms, the specification is not enabling. However, the claims do not recite that the purified stereoisomer be in the *cis* or *trans* form so that this point is irrelevant with respect to a procedure for separating diastereomers. Also, there is a constant interconversion between the *cis* and *trans* isomers so even if one were to isolate the *trans* isomer it would quickly convert to a mixture of *cis* and *trans* isomers. Applicant submits that the claims do not mention *cis* and *trans* forms of the claimed compounds; therefore, the specification does not need to provide a procedure for separating the *cis* and *trans* isomers of these compounds. The Applicant is claiming mixtures enriched in peptides containing L-boroproline (*e.g.*, L-Ala-L-boroPro, L-Pro-L-boroPro) and not mixtures enriched in the *cis* or *trans* isomers (*e.g.*, *cis*-L-Ala-L-boroPro, *trans*-L-Ala-L-boroPro). Therefore, Applicant does not have to provide a method for obtaining the *cis* and *trans* isomers for the claimed invention to be enabled.

The Examiner is also concerned about the silica gel chromatography method described on page 15, starting at line 3 and how it would be read by one of ordinary skill in the art. The silica gel-based method was initially thought by the inventors to be able to separate the diastereomers of boroproline-containing peptides; however, further study of the purified products revealed that the silica gel method separated the *cis* and *trans* isomers rather than the diastereomers. The inventors hesitation in concluding that conventional silica gel chromatography could separate diastereomers is indicated by the words "appears" and "probably" in the two concluding sentences of that paragraph. Since silica gel chromatography is usually not able to resolve diastereomers, it is reasonable to assume that a chemist reading this paragraph would also be hesitant in believing that this method would separate the diastereomers of boroproline-containing peptides. HPLC is a much more commonly used chromatographic method for separating diastereomers since there is only a small difference between the diastereomers to be separated. The higher resolution of HPLC is necessary to separate molecules with only subtle differences such as diastereomers, as would be appreciated by one of skill in this art.

Biological Chemistry and Molecular Pharmacology at Harvard Medical School, Boston.

Massachusetts, was submitted on October 7, 2002, in the above-referenced case. Declarant Rando in paragraph 7 states "that the description of the invention in the applications is sufficient to allow a chemist of ordinary skill to make and use the claimed boroproline-containing L isomers." Rando states that the equivocal language such as "appears" and "probably" suggests that the procedure on page 15 is not the definitive procedure for purifying the L isomer of a boroproline-containing peptide and that the procedure on page 21 unambiguously states that HPLC C_{18} chromatography can be used to separate the L and D isomers. The Examiner in the latest Office Action contradicts Rando without any evidence. The Examiner states that the "question is what the skilled chemist reading the specification would have concluded about what applicant has done"; however, then the Examiner completely ignores what Rando, a skilled chemist, has said and instead goes on saying "the skilled chemist reading pages 15 and 21 would not have concluded that the C_{18} chromatographic method of page 21 would have succeeded, while at the same time, the silica get chromatographic method of page 15 of the specification would have failed." The Examiner makes this conclusion without any evidence and seems to base his statement on his own personal beliefs.

The Examiner has improperly raised the separation of *cis* and *trans* isomers as a basis for non-enablement of the claimed invention and fails to make a *prima facie* case. The Examiner has also relied on unsupported assertions that the specification contains errors that render the specification non-enabling. Applicant has submitted evidence to the contrary in the form of a Declaration from Professor Rando, a skilled chemist. This evidence is sufficient to rebut the unsupported assertions of the Examiner regarding the understanding of one of ordinary skill in the art having read the specification. Withdrawal of the rejection of claims 35, 36, 39-43, and 46-51 for lack of enablement is respectfully requested.

II. Rejection under 35 U.S.C. § 112, first paragraph, for lack of written description is unwarranted given the disclosure in the specification of stereochemical purities between 96% and 99%.

Claims 35, 36, 39-43, and 46-51 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time application was filed, had possession of the claimed invention. The Examiner has concluded that support for the limitation that "the stereochemical purity of the carbon atom bearing boron exceeds 96%" is lacking. In support of these conclusions, the Examiner asserts that "applicants have pointed to the declaration filed 10/10/02, wherein it is stated that the designation "99-6%" is consistent with an interpretation that a range 96-99% is intended." Examiner argues that "the designation "99-6%" is even more consistent with the interpretation of 99.6%" even though this interpretation would require changing the dash in the specification into a decimal point. The Examiner also maintains that "in normal English usage, the lower number is presented first, *i.e.*, 96-99%, rather than 99-96%."

Applicant respectfully submits that this rejection for lack of written description was made for the first time nearly seven years after the filing date of the priority application. The present application is a continuation of USSN 08/459,654, filed June 2, 1995, now abandoned. The issues which now have been raised as a basis for the rejection of claims under § 112, first paragraph, were ones which could have been raised by the Examiner as early as 1998 during prosecution of the parent application and/or this present continuation application. In particular, the limitation relating to "at least 96% of the carbon atoms bearing boron are of the L configuration" was present in USSN 08/950,452, claim 35, as added on September 4, 1998. Indeed, as early as June 24, 1999 (Office Action mailing date in USSN 08/950,452), Examiner Lukton on page 8 *recommended* that Applicant consider adding a new claim 52 to the further the discussion of allowable subject matter (emphasis added):

> 52. A method of obtaining a mixture consisting of two or more stereoisomers of formula I
>
> [illegible]
>
> resulting mixture *at least 96% of the carbon atoms bearing boron are of the L configuration.*

Certainly, if the Examiner recommended using the language appearing in italics in proposed claim 52, he must have considered such language supported by the specification at the time the recommendation was made. In the interval since the Examiner recommended new claim 52, additional Office Actions have issued; however, the Examiner did not object to the language relating to greater than 96% until March 15, 2001. The Office Action mailed on March 15, 2001 was the first to issue after an in-person interview was held in Washington to discuss the § 103 rejection.

Applicant herein again reiterates that the range "99-6%" on page 21 supports the limitations 96% and 99% as found in claims 35, 39, 42, and 46. A dash is a dash and should be interpreted as such. A dash is not a decimal point. The phrase should be construed to mean 99%-6% or 99%-96%, and the only reasonable interpretation is 99%-96% as 6% pure would hardly be a purity which the Applicant could have been attempting to achieve. To change a dash into a decimal point is to rewrite the Specification. The Examiner is essentially rewriting the Applicant's Specification to make the dash a decimal point in order to support his argument and thereby deny the Applicant his patent right. The Examiner should not be permitted to rewrite the language written as opposed to interpret the language.

In addition, in support of the Applicant's interpretation of the designation "99-6%", applicant has submitted a Declaration by Professor Rando stating in paragraph 9 that "although it is conventional to place the lower value number first in giving a range, the expression "99-6%" is consistent with an interpretation that the phrase "99-6%" refers to a range of about 96% to 99%." Paragraph 9 of the Rando Declaration concludes with Rando stating that "the description of the invention would be understood by a practicing scientist."

The Examiner raises the issue of support for the limitations, "at least 96%" and "99%", but fails to make a prima facie case that the specification does not provide support for this limitation. Instead, the Examiner relies upon unsupported assertions that the meaning of the phrase, "99-6%", in the specification is not normal English usage and that the designation "99-6%" is even more consistent with the interpretation of 99.6%. Respectfully, the Examiner's

sufficiency of the disclosure for satisfying 35 U.S.C. § 112, first paragraph. The only legal issue

for consideration that is relevant to this rejection is whether the specification contained a description of the claimed invention so as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. The Declaration of Professor Rando is sufficient to rebut the unsupported assertions regarding the understanding of one of ordinary skill in the art with respect to the description of the invention.

In summary, three Office Actions issued in the pending application between when the greater than 96% limitation was introduced into the claims and when the claims were rejected for lack of written description for this language. Approximately two and half years passed between introduction of the limitation into the claims and when the Examiner first rejected the claims for lack of written description. Applicant is entitled to timely prosecution of this Application Certainly, if the specification's teachings were as lacking as characterized by the Examiner, this issue would have been raised early on in the prosecution of the present application and the Examiner would not have included this language in a proposed claim. Withdrawal of the rejection of claims 35, 36, 39-43, and 46-51 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

III. Rejection under 35 U.S.C. § 103, as being unpatentable over Bachovchin (*J. Biol. Chem.* 265:3738, 1990), is improper since the reference is non-enabling.

Claims 35, 36, 39, 41, 42, 46, and 47-49 are rejected under 35 U.S.C. § 103 as being unpatentable over Bachovchin (*J. Biol. Chem.* 265:3738, 1990). The basis for this rejection is reproduced below:

"As indicated previously, Bachovchin teaches (page 3743, col 1, paragraph 3) acquisition of the requisite isomer, but that the purity was only 95%. If the requisite isomer can be obtained with 95% purity after only one pass through a column, an organic chemist of ordinary skill would have expected that a purity of at least 96% could be obtained after two passes. In response applicants have pointed to the declaration (paper No. 58, filed 10/10/02), in which it is stated (paragraph 10) that the skilled chemist would have been motivated to isolate and use the

skilled chemist would have been motivated to use the D isomer because of its greater *in vivo* lifetime."

The arguments of record are reiterated here. Applicant has repeatedly explained to the Examiner in writing and in person the reasons why the Bachovchin JBC reference does *not* teach or suggest a method for separating the L and D isomers at all, let alone to 95% purity, and has provided two Declarations from William Bachovchin, an inventor on the present application and an author of the Bachovchin JBC reference, and one Declaration from Robert R. Rando to establish that the Bachovchin reference does *not* teach a method of separating these isomers. In total, three Declaration have been properly submitted stating the Bachovchin JBC reference does not teach an effective method of separating the L and D isomers of the claimed compounds; however, the Examiner still maintains this rejection. Applicant believed this issue to have been finally resolved following the interview at the U.S. Patent and Trademark Office held in 2001 when the Examiner correctly summarized the evidence of record and Applicant's related arguments in the Interview Summary (emphasis added):

> "Applicant argued that separation of the "D" + "L" isomers not a straightforward matter + that the assertion of such separation in Bachovchin (1990) was incorrect. Accordingly, the D/L separation is "unexpected". *The Examiner stipulated that the evidence presented indicates that the assertion in Bachovchin JBC 1990 of such separation was incorrect.*"

The Bachovchin Declaration evidences that the Bachovchin reference does not teach a method for separating the D and L isomers of boroproline-containing peptides. Accordingly, repeatedly using the procedure from the Bachovchin reference by passing a sample through the disclosed column multiple times will not result in the separation of the D and L isomers. Applicant does not understand how the Patent Office can stipulate that the reference fails to teach an effective method for separating the D and L isomers and then say the opposite later. As with the new § 112 issue raised after years of prosecution, Applicant is entitled to timely prosecution of its Application and Applicant should be able to rely on written statements by the Examiner. The Examiner conceded the point previously, Declaration evidence has been submitted as proof of the same point and that evidence is unrebutted. The Examiner has not met his burden in continuing to reject the claims on this basis. This issue should be resolved in Applicant's favor for these reasons alone.

replacing L-isomers with D-isomers results in loss of activity when the compound at issue is a

peptide inhibitor of a protease." First, this rationale fails because the prior art does not teach how to obtain the purified diastereomers, as pointed out above. Second, the Examiner's statement is without support in the record and therefore is insufficient to make out a *prima facie* case for rejecting the claims. Separately, the generalized assertion that L-isomers have greater biological activity than D-isomers also is an insufficient basis to motivate one with ordinary skill in the art to select L-isomers over their D-counterparts. Better biological activity is not the only factor involved in selecting a therapeutic. Biological half-life, for example, can be equally important in selecting one versus another isomer. D-isomers would be expected to have a greater half-life than L-isomers as established by the Declaration of Professor Rando. The motivation might exist to examine whether one on the whole is better than the other, but there is no support in the record that there is motivation to pick the L-isomer over the D-isomer as suggested by the Examiner. The motivation for purposes of establishing a *prima facie* case of obviousness must have support and must have a nexus to the claimed invention. In the face of such unsupported assertions regarding the superiority of L-isomers over D-isomers, there is no basis for the Examiner to conclude that one of ordinary skill in the art would be more motivated to select one isomer over the other.

Even if one skilled in the art were motivated to separate and select the L-isomer of boroproline (which Applicant disputes), there is still no teaching or suggestion in the art as to how one would accomplish this separation. Indeed, the Bachovchin JBC reference (1990) might be construed as suggesting the use of conventional silica gel chromatography to separate the L- and D-isomers; however, this method does not work. A chemist reading the Bachovchin reference would be motivated to try the conventional silica gel chromatography to separate the L- and D-isomers of boroproline because the reference explicitly refers to such a protocol, and in fact, he or she would not be motivated to attempt to use another method such as HPLC unless he or she independently discovered that the suggested conventional silica gel chromatography method was not effective. And even then, one of ordinary skill in the art would not have been pointed toward a successful solution to the problem by the prior art.

The Examiner appears to take the position that at the time this invention was made, C[illegible]

[illegible] alleged that alternative methods to HPLC would not have been used because they were less

effective. In addition, the Examiner appears to take the position that once the skilled chemist decided to use HPLC, he naturally would have selected a C_{18} column for the separation and the appropriate solvents as the eluant. Again, no evidence beyond an assertion of the wide availability of C_{18} columns is provided to support this assertion. As discussed below, these assertions are insufficient to establish a *prima facie* case of obviousness and are rebutted by the evidence of record. The Examiner not only fails to make out a *prima facie* case in the first instance, but the Examiner also fails to rebut the affirmative evidence made of record in response to the unsupported arguments made by the Examiner. The issue of non-obviousness should be decided in Applicant's favor for these reasons alone.

The prior art and particularly the Bachovchin JBC reference does not provide the motivation required by law to modify the references in the manner suggested by the Examiner to obtain the claimed invention. There is no teaching or suggestion in the cited art to select the L-isomers of boroproline over the D-isomers of boroproline or of the means to obtain a mixture of isomers that contains at least 96% L-isomer. Indeed, there is no teaching in any of the references cited by the Examiner for separating L from D isomers for any compound. Accordingly, at the time the invention was made, there would have been no motivation to modify the cited art to further purify L isomers in the manner suggested by the Examiner. Moreover, even if one were motivated to select the L isomer of boroproline, one skilled in the art would not have had the requisite expectation of success to render the claimed invention *prima facie* obvious. These deficiencies in the cited references cannot be cured by the Examiner's assertions of motivation to select the L-isomers and to use C_{18} HPLC to effect the separation. Accordingly, there is no motivation to modify any of the references as suggested by the Examiner to obtain the claimed invention.

As further evidence to support the Applicant's argument that one of ordinary skill in this art would not have been motivated to isolate the L-isomer and would not have had the means to do so at the time the invention was made, Applicant has submitted a Declaration by Professor Robert R. Rando of Harvard Medical School. In paragraph 10 of the Declaration, Rando declares that "one skilled in the art would expect the D-isomer to have a longer half-life in vivo."

[illegible] reduced potency compared to the L-isomers." Rando in paragraph 11 disagrees with the

Examiner's assertion "that one skilled in the art would have been motivated to use HPLC C18 chromatography to purify the boroproline-containing L isomers at the time the invention was made and also would have had a reasonable expectation that this method would be useful for achieving purification of the L isomer." The declarant expands upon this point by adding that "although HPLC C18 columns were in general use at the time the priority application was filed (October 1991), a variety of purification techniques, such as HPLC using fine bore silica, chromatography using chiral matrix materials to separate stereoisomers, HPLC using other types of resins such as C8 columns, ion-exchange chromatography, and thin layer chromatography also were available." Therefore, Rando, as one of ordinary skill in the art, has declared that there would have been no motivation to use the L-isomer over the D-isomer and in addition there would have been no motivation to use C_{18} HPLC to effect the separation.

In view of the limited teachings of the Bachovchin JBC reference and the Rando Declaration, it would not have been obvious to modify the teachings of the cited art in the manner suggested by the Examiner because: (1) there is no *evidence* of record to support the motivation for one of ordinary skill in the art to select the L isomer; (2) even if one were motivated to make such a selection, one of ordinary skill in the art would not have had a method for separating the L from the D isomer; (3) there was no reasonable expectation of success that one could effectively separate L from D isomers to obtain the claimed composition; and (4) the Rando Declaration evidence supports a conclusion that even if one had attempted to use the purified L isomer, such efforts would not have had a reasonable expectation of success.

Applicant respectfully requests closure on this issue and withdrawal of the rejection of claims under 35 U.S.C. § 103 as obvious in view of the Bachovchin JBC reference.

Conclusion

Appellant respectfully submits that the invention of claims 35, 36, 39-43, and 46-51 is described in the specification in such a way to enable one skilled in this art to make and use the claimed invention and in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed had possession of the claimed invention. The JBC reference by Bachovchin *et al.* also does not render obvious the claimed invention for the various reasons set forth above. Allowance of the pending claims is therefore requested.

A check in the amount of $160.00 for filing the Appeal Brief is enclosed herewith. If there are any additional charges, or any credits, please apply them to our Deposit Account Number 03-1721.

Respectfully submitted,

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Typed or Printed Name of person signing certificate

Attachment I

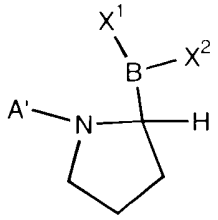
to

Appeal Brief under 37 C.F.R. § 1.192

Claims on Appeal

Claims on Appeal

35. (Thrice Amended) A mixture of stereoisomers consisting of a compound of the following structure and at least one stereoisomer thereof:



wherein each X^1 and X^2 is, independently, a hydroxyl group or a group that is hydrolyzed to a hydroxyl group at physiological pH;

wherein at least 96% of the carbon atoms bearing boron are of the L-configuration;

wherein A' comprises an amino acid; and

wherein each of the compounds inhibits DP-IV activity.

36. (Amended) The mixture of claim 35, wherein X^1 and X^2 are hydroxyl groups.

37. (Cancelled)

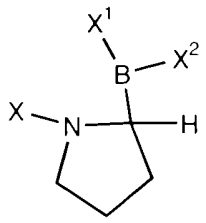
38. (Cancelled)

39. (Amended) The mixture of claim 35, wherein 99% of the carbon atoms bearing boron are of the L-configuration.

40. (Amended) The mixture of claim 35, wherein A' is valine.

[illegible]

[illegible] (Thrice Amended) A mixture of stereoisomers consisting of a compound of the following structure and at least one stereoisomer thereof:



wherein each X^1 and X^2 is, independently, a hydroxyl group or a group that is hydrolyzed to a hydroxyl group at physiological pH;

wherein at least 96% of the carbon atoms bearing boron are of the L-configuration;

wherein X comprises an amino acid or a peptide; and

wherein each of the compounds inhibits DP-IV activity.

43. (Amended) The mixture of claim 42, wherein X^1 and X^2 are hydroxyl groups.

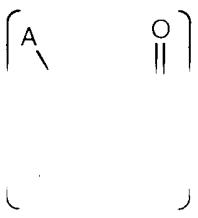
44. (Cancelled)

45. (Cancelled)

46. (Amended) The mixture of claim 42, wherein 99% of the carbon atoms bearing boron are of the L-configuration.

47. (Amended) The mixture of claim 42, wherein X is an L-amino acid.

48. (Amended) The mixture of claim 43, wherein X is a peptide having the structure



wherein m is an integer between 0 and 10, inclusive; and

wherein A and A' are L-amino acid residues such that the A in each repeating bracketed unit can be the same or a different amino acid residue.

49. (Amended) The mixture of claim 48, wherein A and A' are independently proline or alanine residues.

50. (Amended) The mixture of claim 48, wherein m is an integer between 1 and 10.

51. (Amended) The mixture of claim 48, wherein m is 1.